



Ottawa Hull K1A 0C9



(11) (C) 1,339,452
(21) 602,683
(22) 1989/06/13
(45) 1997/09/09
(52) 260-363
C.L. CR. 167-245

(51) Int.Cl. 6 C07D 307/87; A61K 31/34

(19) (CA) **CANADIAN PATENT (12)**

(54) Enantiomers of Citalopram and Derivatives Thereof

(72) Boegesoe, Klaus Peter , Denmark
Perregaard, Jens , Denmark

(73) H. LUNDBECK A/S , Denmark

(30) (GB) U.K. 88 14057 1988/06/14

(57) 11 Claims

NO DRAWING



Industrie
Canada Industry
Canada

OPIIC - CIPO 191

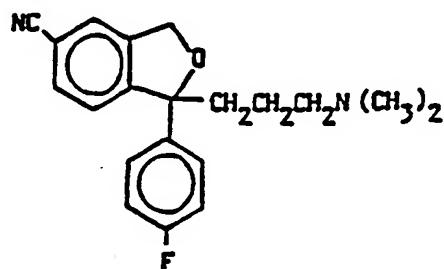
Canada

BEST AVAILABLE COPY

SEP - 9 1997 1339452

Abstract of the Disclosure

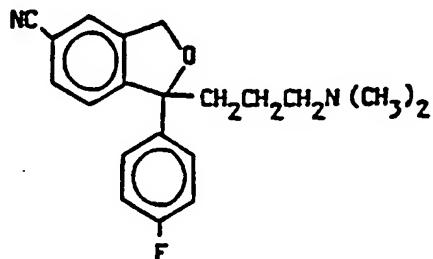
The present invention relates to the two novel enantiomers of the antidepressant drug 1-(3-dimethylaminopropyl)-1-(4'-fluorophenyl)-1,3-dihydroisobenzofuran-5-carbonitrile (citalopram) of the following formula I:



and to the use of these enantiomers as antidepressant compounds as well as the possible use as geriatrics or in the cure of obesity or alcoholism.

ENANTIOMERS OF CITALOPRAM AND DERIVATIVES THEREOF

The present invention relates to the two novel enantiomers of the antidepressant drug 1-(3-dimethylaminopropyl)-1-(4'-fluorophenyl)-1,3-dihydroisobenzofuran-5-carbonitrile (citalopram) of the following formula I:



5 and to the use of these enantiomers as antidepressant compounds as well as the possible use as geriatrics or in the cure of obesity or alcoholism.

This invention also includes pharmaceutically acceptable salts of the enantiomers of compound I formed with non-toxic organic or inorganic acids. Such salts are easily prepared by methods known to the art. The base is reacted with either the calculated amount of organic or inorganic acid in an aqueous miscible solvent, such as acetone or ethanol, with isolation of the salt by concentration and cooling or an excess of the acid in aqueous immiscible solvent, such as ethyl ether, ethyl acetate or dichloromethane, with the desired salt separating directly. Exemplary of such organic salt are those with maleic, fumaric, benzoic, ascorbic, pamoic, succinic, oxalic, salicylic, methanesulfonic, ethanesulfonic, acetic, propionic, tartaric, citric, gluconic, lactic, malic, mandelic, cinnamic, citraconic, aspartic, stearic, palmitic, itaconic, glycolic, p-amino-benzoic, glutamic, benzene sulfonic and theophylline acetic acid, as well as the 8-halotheophyllines, for example 8-bromotheophylline. Exemplary of such inorganic salts are those with hydrochlo-

X



ric, hydrobromic, sulfuric, sulfamic, phosphoric and nitric acids. Of course, these salts may also be prepared by the conventional method of double decomposition of appropriate salts, which is well-known to the art.

5 Furthermore it was found that non-hygroscopic acid addition salts might be obtained by conventional freeze drying techniques from water solutions of appropriate salts of the above mentioned kinds.

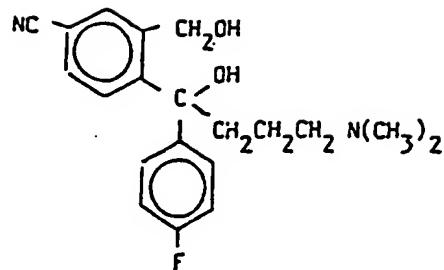
10 The invention is also concerned with a method to resolve the racemate of I into the individual isomers.

BACKGROUND OF THE INVENTION

Citalopram, which has been disclosed in eg. US Patent No. 4,136,193, has proven to be an efficient antidepressant compound in man (Ref.: A. Gravem et al., Acta Psychiat. Scand., No. 75, p. 478-486 (1987)). All work in the development of this compound has been made with the racemate. Citalopram has been shown pharmacologically to be a very selective inhibitor of 5-HT reuptake. Previous attempts to crystallize diastereomeric salts of citalopram enantiomers have failed.

SUMMARY OF THE INVENTION

Surprisingly, it has now proven possible to resolve the intermediate 4-[4-(dimethylamino)-1-(4'-fluorophenyl)-1-hydroxy-1-butyl]-3-(hydroxymethyl)-benzonitrile II, into its enantiomers and finally in a stereoselective way to convert these enantiomers to the corresponding citalopram enantiomers. Likewise, monoesters of II formed by optically active carboxylic acids could be separated into the corresponding diastereomers and subsequently converted directly into citalopram enantiomers in a stereoselective ringclosure reaction. The intermediate diol, II, has been disclosed in eg. US Patent No. 4,650,884 as a racemic mixture.



II

The enantiomers of the intermediate of formula II as well as monoesters fall likewise within the scope of the present invention.

Furthermore, it was shown to our surprise that almost the entire 5-HT uptake inhibition resided in the (+)-citalopram enantiomer.

The present invention also includes a new method of synthesizing I from the diol compound II by esterification of the primary alcohol group into a labile ester, which in the presence of a base undergoes spontaneous ringclosure to citalopram or, if enantiomerically pure II is esterified, the corresponding citalopram enantiomer is produced with fully conservation of stereoconfiguration.

According to the invention, II is reacted with:

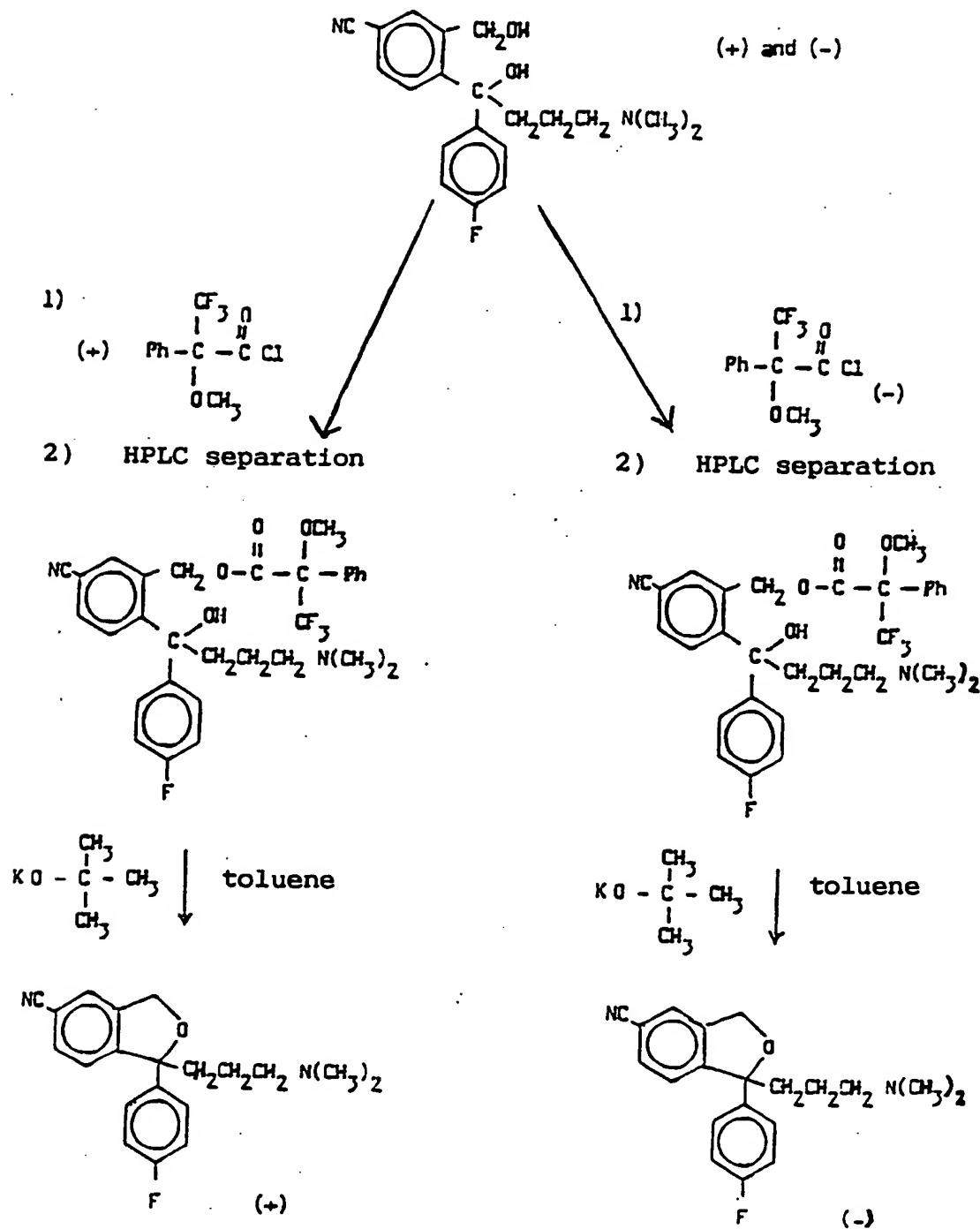
a)

an enantiomerically pure acid derivative as an acid chloride, anhydride or labile ester as eg. exemplified in reaction scheme I by (+)- or (-)- α -methoxy- α -trifluoromethylphenylacetyl chloride. The reaction is preferably performed in an inert organic solvent as eg. toluene, dichloromethane or tetrahydrofuran. A base (triethylamine, N,N-dimethylaniline, pyridin or the like) is added to neutralize liberated HCl. The diastereoisomers are subsequently separated by HPLC or fractional crystallization. The thus purified diastereoisomers are finally separately treated with strong base (eg. alkoxide) in an inert organic solvent as eg. toluene, tetrahydrofuran, or dimethoxyethane yielding the pure citalopram enantiomers respectively. The ringclosure reaction is preferably performed at relatively low temperatures (-20°C to room temperature).

X

1339452

REACTION SCHEME I



X

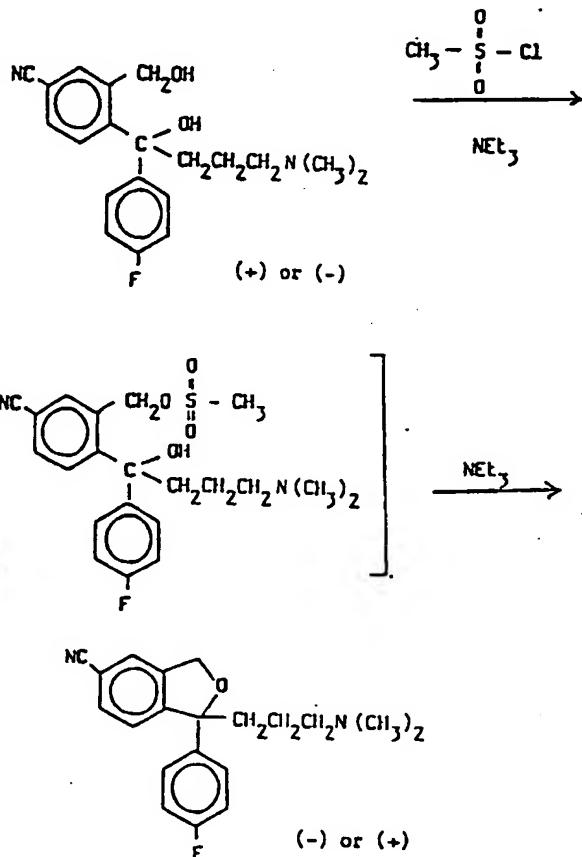
b)

the enantiomers of an optically active acid successively affording the pure diastereomeric salts. Optically antipodes of tartaric acid, di-benzoyltartaric acid, di-(p-toloyl)tartaric acid, bisnaphthylphosphoric acid, 10-camphorsulphonic acid and the like are conveniently used.

5
c)

10 Stereoselective ringclosure of the pure enantiomers of II prepared as in b) is performed via a labile ester as eg. methansulfonyl, p-toluenesulfonyl, 10-camphorsulfonyl, trifluoroacetyl or trifluoromethansulfonyl with simultaneous addition of a base (triethylamine, dimethylaniline or pyridin) in an inert organic solvent at 0°C. The ring-closure reaction is exemplified in reaction scheme II:

15

REACTION SCHEME II

X

EXAMPLE 1Resolution by method a)

To 11 g of (+)- α -methoxy- α -trifluoromethylacetic acid dissolved in 25 ml of chloroform were added 50 ml of thionylchloride and a few drops of dimethylformamide. The reaction mixture was refluxed for 2 hours. Excess of thionylchloride was evaporated with toluene leaving the (+)- α -methoxy- α -trifluoromethylacetyl chloride as a liquid. This liquid diluted with 50 ml of dichloromethane was added dropwise to an ice cooled solution of 17 gr of 4-[4-(dimethylamino)-1-(4'-fluorophenyl)-1-hydroxy-1-butyl]-3-(hydroxymethyl)-benzonitrile II, and 8 ml of triethylamine in 150 ml of dichloromethane. The reaction mixture was further stirred for another hour at room temperature, subsequently washed with brine, dried ($MgSO_4$) and the solvent evaporated below 30°C in vacuo affording 29 gr of the ester as a diastereomeric mixture. By repeated HPLC purification (eluted with ethyl acetate / tetrahydrofuran 9:1 containing 4% of triethylamine) and by collecting only the 5-10% initial substance in the main peak, 1.1 gr of enantiomerically pure compound was isolated.

The substance thus isolated was dissolved in dry toluene (50 ml) and added to a suspension of 0.3 gr of potassium t-butoxide in 20 ml of toluene at 0°C. The toluene solution was washed with water, dried ($MgSO_4$) and the solvent evaporated yielding 0.6 gr of (+)-1-(dimethylaminopropyl)-1-(4'-fluorophenyl)-1,3-dihydroisobenzofuran-5-carbonitrile as an oil. $[\alpha]_D = +11.81^\circ$ ($c = 1, CH_3OH$) (determined with a substance containing 10% w/w of methanol). The optical purity was determined by 1H NMR spectroscopy ($CDCl_3$ as solvent) (Bruker AC-250 MHz instrument) by addition of a 10:1 w/w surplus of the chiral reagent (-)-2,2,2-trifluoro-1-(9-anthryl)ethanol. Optical purity: 99.6%.

In a totally analogous way the (-)-1-(3-dimethylaminopropyl)-1-(4'-fluorophenyl)-1,3-dihydroisobenzofuran-5-carbonitrile was synthesized. $[\alpha]_D = -12.34^\circ$ ($c = 1, CH_3OH$) (determined with a substance containing 10% w/w of methanol). Optical purity: 99.9%.

B |

EXAMPLE 2Resolution by methods b) and c)

To a solution of 85 gr of 4-[4-(dimethylamino)-1-(4'-fluorophenyl)-1-hydroxy-1-butyl]-3-(hydroxymethyl)-benzonitrile, hydrobromide in 500 ml of water were

5 added 200 ml of ice cooled 2 M NaOH solution and 500 ml of ether. The mixture was stirred for 1/2 hour, the ether phase separated, dried ($MgSO_4$) and the ether evaporated. The remaining oil was dissolved in 400 ml of 2-propanol at $40^\circ C$, and 40 gr of (+)-di-p-tolyltartaric acid (as hydrate) were added under vigorous stirring. After a short while crystallization began. After 3 hours of stirring the precipitated salt was filtered off and dried yielding 29.2 gr (55.1%) of (-)-4-[4-(dimethylamino)-1-(4'-fluorophenyl)-1-hydroxy-1-butyl]-3-(hydroxymethyl)-benzonitrile

10 hemi (+)-di-p-tolyltartaric acid salt. MP: $134-135^\circ C$, $[\alpha]_D = +10.0^\circ$ ($c = 1$, CH_3OH). The filtrate is used below.

15 To an ice cooled solution of 14 gr of the (-)-isomer from above as a base in 300 ml of dry toluene were added 16 ml of triethylamine, and 3.6 ml of methansulfonyl chloride in 20 ml of dry toluene were added dropwise during 10 minutes. The reaction mixture was further stirred for 1/2 hour, washed with brine, dried ($MgSO_4$) and the solvent evaporated. The title compound was purified by column chromatography affording 8 g of (+)-1-(3-dimethylaminopropyl)-1-(4'-fluorophenyl)-1,3-dihydroisobenzofuran-5-carbonitrile. $[\alpha]_D = +12.33^\circ$

20 ($c = 1$, CH_3OH).

The oxalic acid salt of the (+)-isomer crystallized from acetone. MP: $147-148^\circ C$, $[\alpha]_D = +12.31^\circ$ ($c = 1$, CH_3OH).

25 The pamoic acid salt of the (+)-isomer was prepared in the following manner: To 1.8 g of the base of the (+)-isomer was added 2 g of pamoic acid in 25 ml of MeOH. The mixture was refluxed for an hour and subsequently cooled to room temperature. The precipitate was filtered off yielding 3.0 g of the pamoic acid salt. MP: $264-266^\circ C$, $[\alpha]_D = +13.88^\circ C$ ($c = 1$, dimethylformamide).

30 A 2:1 addition compound of the (+)-isomer with L(+)-tartaric acid was prepared in the following manner: 4 g of the (+)-isomer as base were dissolved in 100 ml of diethyl ether and extracted into 100 ml of water containing 0.8 g of L(+)-tartaric acid by stirring. The organic phase was separated and discarded. The waterphase

was freeze-dried in vacuo (< 0.1 mm Hg) for 18 hours leaving 3.8 g of a white powder of the title compound. This addition compound was stable and not hygroscopic.

In a corresponding manner as above via the (+)-4-(dimethylamino)-1-(4-fluorophenyl)-1-hydroxy-1-butyl-3-(hydroxymethyl)-benzonitrile, hemi (-)-di-(p-toyloyl)tartaric acid salt ($[\alpha]_D = -8.9^\circ$ (c = 1, CH₃OH)) which was converted to the corresponding diol base ($[\alpha]_D = +61.1^\circ$ (c = 1, CH₃OH)) and finally ringclosure reaction yielded 10 gr of (-)1-(3-dimethylaminopropyl)-1-(4'-fluorophenyl)-1,3-dihydroisobenzofuran-5-carbonitrile. $[\alpha]_D = -12.1^\circ$ (c = 1, CH₃OH).

The oxalic acid salt of the (-)-isomer crystallized from acetone. MP: 147-148°C, $[\alpha]_D = -12.08^\circ$ (c = 1, CH₃OH).

EXAMPLE 3

Preparation of citalopram by method c)

To an ice cooled solution of 28 gr of racemic diol base, II, in 500 ml of dichloromethane were added 32 ml of triethylamine, and 7.5 ml of methanesulfonyl chloride in 30 ml of dichloromethane were added dropwise during ½ hour. The reaction mixture was washed with 0.1 M NaOH solution twice, the organic phase separated, dried (MgSO₄) and the solvent evaporated, leaving 21.5 gr of the title (-)-citalopram as a crystalline base. The thus obtained material was dissolved in a mixture of 2-propanol and methanol (2:1) and an equivalent amount of gaseous HBr was introduced. The mixture was left overnight and the precipitated hydrobromide was filtered off. Yield: 26 gr with MP 184-186°C.

The enantiomers from Example 1 were tested for their ability to block 5-HT reuptake in standard and reliable test method. Results are shown in Table I in comparison with the racemic mixture of citalopram.

B

5-HTP-POTENTIATION

The test evaluates the ability of the substance to potentiate the effect of 5-HTP, which results in development of 5-HT syndrome (Christensen, Fjalland, Pedersen, Danneskiold-Samsøe and Svendsen; European J. Pharmacol. 41, 153-162, 1977).

Procedure

Each treatment group consists of 3 mice, and two groups are treated with the highest test dose. A control group only treated with 5-HTP is included and a group treated with citalopram 10 mg/kg and 5-HTP is used as reference for full 5-HT syndrome

The route of administration

30 minutes after the administration of the test substance, the other groups are given 5-HTP (100 mg/kg) i.v. (injection time 5-10 sec.). After this 5-HTP dose normal, untreated mice remain unaffected, but if the animals have been pretreated with a substance, which inhibits the uptake of 5-HT or a 5-HT agonist, a 5-HT syndrome will occur. The symptoms are the same as previously described: 1) excitation, 2) tremor, and 3) abduction of the hind limbs. The animals are observed for 15 minutes and each animal is given one point for each symptom present. Again the result is stated in fractions: 0/9, 1/9, ..., 9/9, where 0, 1, ..., 9 are the number of points per group after the dose in question. The ED₅₀ value is calculated by log-probit analysis.

INHIBITION OF ³H-SEROTONIN UPTAKE IN RAT BRAIN SYNAPTOSONMES

By this method the inhibition by drugs of the uptake of ³H-serotonin (³H-5-HT) (10 nM) in rat brain synaptosomes is determined in vitro. Method and results in Hyttel, Psychopharmacology 1978, 60, 13-18; Hyttel, Prog.Neuro-Psychopharmacol. & Biol.Psychiat. 1982, 6, 277-295; Hyttel & Larsen, Acta pharmacol. tox. 1985, 56, suppl. 1, 146-153.

Procedure

Male Wistar (Mol:Wist) rats (125-250 g) are sacrificed by decapitation and exsanguinated. Brain tissue (minus cerebellum) is gently homogenized (glass teflon homogenizer) in 40 vol (w/v) of icecold 0.32 M of sucrose containing 1 mM of nialamide. The P₂ fraction (synaptosomal fraction) is obtained by centrifugation (600 g, 10 min and 25000 g, 55 min, 4°C) and suspended in 800 volumes of a modified Krebs-Ringer™-phosphate buffer, pH 7.4.

To 4000 µl of the synaptosomal suspension (5 mg original tissue) on ice are added 100 µl test substance in water. After preincubation at 37°C for 5 min, 100 µl of ³H-1-NA (final concentration 10 nM) are added and the samples are incubated for 10 min at 37°C. The incubation is terminated by filtering the samples under vacuum through Whatman™ GF/F filters with a wash of 5 ml buffer containing 10 µM of unlabelled 5-HT. The filters are placed in counting vials and 4 ml of appropriate scintillation fluid (e.g. PicoFluor™ 15) are added. After shaking for 1 h and storage 2 h in the dark the content of radioactivity is determined by liquid scintillation counting. Uptake is obtained by subtracting the nonspecific binding and passive transport measured in the presence of 10 µM citalopram (Lu 10-171-B).

For determination of the inhibition of uptake five concentrations of drugs covering 3 decades are used.

The measured cpm are plotted against drug concentration on semilogarithmic paper, and the best fitting s-shaped curve is drawn. The IC₅₀-value is determined as the concentration, at which the uptake is 50% of the total uptake in control samples minus the nonspecific binding and uptake in the presence of 10 µM of citalopram.

Table 1

PHARMACOLOGICAL TEST RESULTS

Compound	5-HTP pot.	5-HT uptake inhibition
	ED ₅₀ µmol/kg	IC ₅₀ (nM)
(+)-citalopram	2.0	1.1
(-)-citalopram	120	150
(±)-citalopram	3.3	1.8

(+)-1-(3-Dimethylaminopropyl)-1-(4'-fluorophenyl)-1,3-dihydroisobenzofuran-5-carbonitrile ((+)-citalopram) and the non-toxic acid addition salts thereof may be administered to animals such as dogs, cats, horses, sheeps or the like, including human beings, both orally and parenterally, and may be used for example in the form of tablets, capsules, powders, syrups or in the form of the usual sterile solutions for injection. - Results upon administration to human beings have been very gratifying.

5

10

15

Most conveniently the compounds of Formula I are administered orally in unit dosage form such as tablets or capsules, each dosage unit containing the free amine or a non-toxic acid addition salt of one of the said compounds in an amount of from about 0.10 to about 100 mg, most preferably, however, from about 5 to 50 mg, calculated as the free amine, the total daily dosage usually ranging from about 1.0 to about 500 mg. The exact individual dosages as well as daily dosages in a particular case will, of course, be determined according to established medical principles under the direction of a physician.

When preparing tablets, the active ingredient is for the most part mixed with ordinary tablet adjuvants such as corn starch, potato starch, talcum, magnesium stearate, gelatine, lactose, gums, or the like.

20

Typical examples of formulas for composition containing (+)-citalopram in the form of an acid addition salt as the active ingredient, are as follows:

I) Tablets containing 5 milligrams of (+)-citalopram
calculated as the free base:

25

30

Compound 20	5 mg
Lactose	18 mg
Potato starch	27 mg
Saccharose	58 mg
Sorbitol	3 mg
Talcum	5 mg
Gelatine	2 mg
Povidone	1 mg
Magnesium stearate	0.5 mg

2) Tablets containing 50 milligrams of (+)-citalopram calculated as the free base:

	(+)-citalopram	50 mg
	Lactose	16 mg
5	Potato starch	45 mg
	Saccharose	106 mg
	Sorbitol	6 mg
	Talcum	9 mg
	Gelatine	4 mg
10	Povidone	3 mg
	Magnesium stearate	0.6 mg

3) Syrup containing per milliliter:

	(+)-citalopram	10 mg
	Sorbitol	500 mg
15	Tragacanth	7 mg
	Glycerol	50 mg
	Methyl-paraben	1 mg
	Propyl-paraben	0.1 mg
	Ethanol	0.005 ml
20	Water	ad 1 ml

4) Solution for injection containing per milliliter:

	(+)-citalopram	50 mg
	Acetic acid	17.9 mg
	Sterile water	ad 1 ml

25 5) Solution for injection containing per milliliter:

	(+)-citalopram	10 mg
	Sorbitol	42.9 mg
	Acetic acid	0.63 mg
	Sodium hydroxide	22 mg
30	Sterile water	ad 1 ml

Any other pharmaceutical tabletting adjuvants may be used provided that they are compatible with the active ingredient, and additional compositions and dosage forms may be similar to those presently used for neuroleptics, analgesics or antidepressants.

5 Also combinations of (+)-citalopram as well as its non-toxic acid salts with other active ingredients, especially other neuroleptics, thymoleptics, tranquilizers, analgetics or the like, fall within the scope of the present invention.

As previously stated, when isolating the enantiomers of citalopram in the form of an acid addition salt the acid is preferably selected so as to contain an anion which is non-toxic and pharmacologically acceptable, at least in usual therapeutic doses. Representative salts which are included in this preferred group are the hydrochlorides, hydrobromides, sulphates, acetates, phosphates, nitrates, methanesulphonates, ethane-sulphonates, lactates, citrates, tartrates or bitartrates, pamoates and maleates of the amines of Formula I. Other acids are likewise suitable and may be employed if desired. For example: fumaric, benzoic, ascorbic, succinic, salicylic, bismethylenesalicylic, propionic, gluconic, malic, malonic, mandelic, canonic, citraconic, stearic, palmitic, itaconic, glycolic, benzenesulphonic, and sulphamic acids may also be employed as acid addition saltforming acids.

20 When it is desired to isolate a compound of the invention in the form of the free base, this may be done according to conventional procedure as by dissolving the isolated or unisolated salt in water, treating with a suitable alkaline material, extracting the liberated free base with a suitable organic solvent drying the extract and evaporating to dryness or fractionally distilling to effect isolation of
25 the free basic amine.

The invention also comprises a method for the alleviation, palliation, mitigation or inhibition of the manifestations of certain physiological-psychological abnormalities of animals, especially depressions by administering to a living animal body, including human beings, an adequate quantity of (+)-citalopram or a non-toxic acid addition salt thereof. An adequate quantity would be from about 0.001 mg to about 10 mg per kg of body weight in each unit dosage, and from about 0.003 milligrams to about 7 milligrams /kg of body weight per day.

1339452

15

It is to be understood that the invention is not limited to the exact details of operation or exact compound or compositions shown and described, as obvious modifications and equivalents will be apparent to one skilled in the art.

The embodiments of the invention in which an exclusive property or privilege is claimed are defined as follows:

- 1 -

A compound selected from substantially pure (+)-1-(3-Dimethylaminopropyl)-1-(4'-fluorophenyl)-1,3-dihydroisobenzofuran-5-carbonitrile and non-toxic acid addition salts thereof.

- 2 -

5 A compound of Claim 1 being the pamoic acid salt of (+)-1-(3-dimethylaminopropyl)-1-(4'-fluorophenyl)-1,3-dihydro-isobenzofuran-5-carbonitrile.

- 3 -

A pharmaceutical composition in unit dosage form useful as an antidepressant comprising a pharmaceutically-acceptable diluent or adjuvant and, as an active ingredient, an effective amount of a compound as defined in Claim 1.

- 4 -

A pharmaceutical composition in unit dosage form useful as an antidepressant comprising a pharmaceutically-acceptable diluent or adjuvant and, as an active ingredient, an effective amount of the compound of Claim 2.

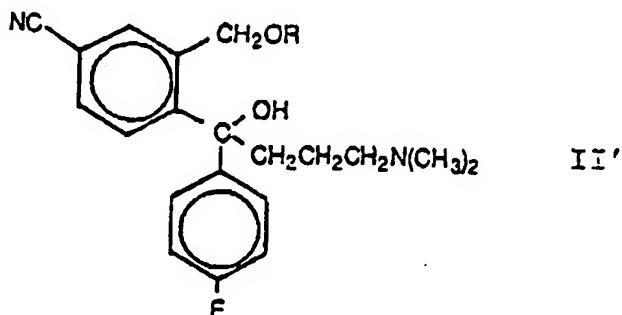
- 5 -

A pharmaceutical composition in unit dosage form, useful as an antidepressant according to claim 3 or 4, wherein the active ingredient is present in an amount from 0.1 to 100 milligram per unit dose.

B

- 6 -

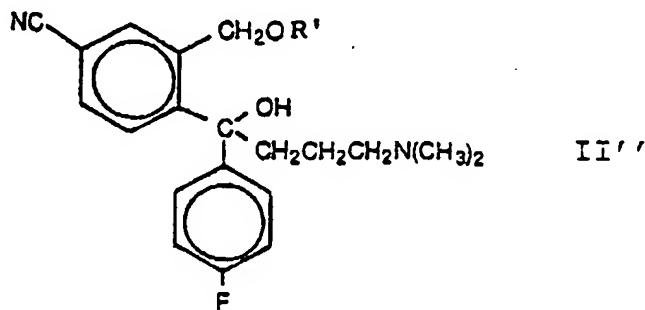
(-) -Enantiomer of the compound 4-[4-(dimethylamino)-1-(4'-fluorophenyl)-1-hydroxy-1-butyl]-3-(hydroxymethyl)-benzonitrile or an ester of said (-) enantiomer, which ester has the general formula



wherin R is an acyl group completing a labile ester.

- 7 -

A method for the preparation of (+)-1-(3-dimethylaminopropyl)-1-(4'-fluorophenyl)-1,3-dihydroisobenzofuran-5-carbonitrile, which comprises the step of resolving the two enantiomers of a compound having the general formula



wherein R' is hydrogen or a labile ester group, thereby obtaining the enantiomer giving (+)-1-(3-dimethylaminopropyl)-1-(4'-fluorophenyl)-1,3-dihydroisobenzofuran-5-carbonitrile, which enantiomer subsequently is cyclized by treatment with base or, if R' is hydrogen, with base in the presence of an acid derivative, which is productive of a labile ester, and then isolating (+)-1-(3-dimethylaminopropyl)-1-(4'-fluorophenyl)-1,3-dihydroiso-

R:

benzofuran-5-carbonitrile as such or as a non-toxic acid addition salt thereof.

- 8 -

A method of Claim 7, wherein the base is selected from triethylamine, dimethylaniline, and pyridine.

- 9 -

A method of Claim 7, wherein the acyl group is selected from methanesulfonyl, p-toluenesulfonyl, 10-camphorsulfonyl, trifluoroacetyl, and trifluoromethanesulfonyl.

- 10 -

A method of Claim 7, wherein the reaction is conducted in an inert solvent.

- 11 -

A method of Claim 7, wherein the reaction is conducted in an inert solvent at 0°C.



{D

**This Page is Inserted by IFW Indexing and Scanning
Operations and is not part of the Official Record**

BEST AVAILABLE IMAGES

Defective images within this document are accurate representations of the original documents submitted by the applicant.

Defects in the images include but are not limited to the items checked:

- BLACK BORDERS**
- IMAGE CUT OFF AT TOP, BOTTOM OR SIDES**
- FADED TEXT OR DRAWING**
- BLURRED OR ILLEGIBLE TEXT OR DRAWING**
- SKEWED/SLANTED IMAGES**
- COLOR OR BLACK AND WHITE PHOTOGRAPHS**
- GRAY SCALE DOCUMENTS**
- LINES OR MARKS ON ORIGINAL DOCUMENT**
- REFERENCE(S) OR EXHIBIT(S) SUBMITTED ARE POOR QUALITY**
- OTHER:** _____

IMAGES ARE BEST AVAILABLE COPY.

As rescanning these documents will not correct the image problems checked, please do not report these problems to the IFW Image Problem Mailbox.